identified in the gene encoding desmin leading to rare diseases belonging to MyoFibrillar Myopathy group (MFM). These pathologies are mainly characterized by aggregates formation in muscle tissue, associated with misorganizations of the contractile apparatus. Moreover patients progressively develop muscle weakness. Currently, pathophysiology and molecular defects of MFMs remain largely unknown, and no treatments are available.
In this context, the aim of our study is to clarify whether desmin mutations implicated in MFMs plays a role at early stage of expression, by impairing the properties of pre-muscular cells, the myoblasts. First we have studied the formation of desmin aggregates in living myoblasts over-expressing for 24h wild-type (WT) or different mutant desmins. We show that each mutant has a specific impact on the desmin network organization. Second we have performed mechanical measurements on C2C12 cells, focusing on the E413K mutant, which induces a large desmin network disorganization associated with important aggregate formation: we have compared the mechanical properties of WT-cells, C2C12 over-expressing desmin-WT-GFP and C2C12 over-expressing mutated desmin E413K-GFP. Visco-elastic properties of cells have been evaluated by using two custom-made set-ups, optical tweezers and a single-cell rheometer: we show that the 3 cells types share the same visco-elastic behaviour. Finally, we have investigated the impact of mutated desmin on the contractility of myoblasts, and we demonstrate that E413K-mutation significantly decreases cell contraction abilities specifically for cells with desmin aggregates, while aggregates of WT-desmin do no induce the same effect.

1801-Pos Board B531
The Cell as a Liquid Motor: Intrinsic Mechanosensitive Properties of the Actomyosin Cortex
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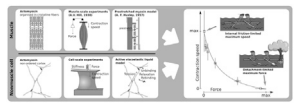
Living cells adapt and respond actively to the mechanical properties of their environment. In addition to biochemical mechanotransduction, evidence exists for a purely mechanical sensitivity to the stiffness of the surroundings at the cell-scale. We show that the mechanosensitive response of cells spreading between distant elastic microplates is entirely and quantitatively predicted by the behaviour of the actomyosin cortex as a contractile viscoelastic fluid. Indeed, such a liquid exhibits elastic-like properties when in series with a spring, and has thus the intrinsic feature of adapting instantaneously its loading rate to the stiffness of its environment. The maintenance of a given shape for such a material results from a balance between actin polymerisation and a cell-scale contractility-driven retrograde flow. The energetic cost of these antagonistic phenomena yields a power curve of cell action against a load similar to Hill's law for muscles: in particular, an internal friction sets the maximum speed of contraction of both cells and muscles, when myosins don't have time to detach after pulling, just as rowers lifting their oar too slowly after their stroke. The figure below illustrates this comparison with muscles.



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The Effects of Out of Plane Curvature on Collective Cell Migration
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Collective cell migration is at play in many well documented in vivo processes for example, wound re-epithelialization, cancer metastasis and dorsal closure. We present a study describing the effect of out of plane curvature on the collective properties of epithelial tissue. Microfabricated environments are used to deconstruct a monolayer's response to geometry. Specifically, fibers with a radius of curvature between 1um-100um are populated with MDCK cells, a model epithelial, kidney-derived, cell line. Migration dynamics as well as cell architecture are quantified and the effects of curvature compared with confinement alone. Large curvatures trigger specific cellular behaviors and organization that may shed light on tubulogenesis.

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A Slipping Clutch in Neuronal Growth Cones Revealed by Transient Single Molecule Interactions between Flowing Actin and N-Cadherin Adhesions
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The molecular clutch model proposes that the actin motile machinery generated inside cells is coupled to adhesion at the cell membrane, thus generating forces on the substrate and allowing cells to move forward. Many reports have provided evidence for clutch-like behaviors in different cell types and adhesive systems, including integrins and cadherins (Giannone et al., Trends Cell Biol 2009). However, the exact mechanisms underlying the dynamic molecular coupling between the actin retrograde flow and adhesion proteins remain elusive. We previously inferred using optical tweezers that a molecular clutch between the actin flow and N-cadherin adhesions could drive growth cone migration (Bard et al., J Neurosci 2008), but did not achieve a direct visualization of the engagement process. Here, to trigger N-cadherin homophilic adhesions at specific locations, we cultured primary neurons on micropatterned substrates comprising arrays of dots coated with purified N-cadherin, surrounded by a cytophobic background. We then tracked the trajectories of single adhesion and cytoskeletal molecules fused with photo-convertible fluorescent proteins (mEOS2), at the ventral surface of growth cones. N-cadherin and α-catenin were immobilized, while the actin retrograde flow was significantly reduced at N-cadherin coated micro-patterns, compared to non-adhesive regions. Normal actin flow on micro-patterns was restored by expression of a dominant negative N-cadherin construct inhibiting the coupling between endogenous N-cadherin and actin, demonstrating specificity of the process. Strikingly, individual actin trajectories exhibited pauses of the order of seconds selectively on N-cadherin-coated micro-patterns. Thus, at the individual molecular level, clutch engagement is characterized by transient interactions between flowing actin filaments and the immobilized N-cadherin/catenin complex. To our knowledge, this study represents the first direct demonstration of the intrinsic molecular coupling underlying the clutch process in growth cone locomotion.

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Molecular Mechanisms of Contractility-Based Cellular Mechanosensing
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Mechanosensing is fundamental to numerous cellular functions, and myosin II is a core component of this mechanosensory machinery. Given the importance of successful cell division for maintaining genomic integrity, we reasoned that myosin II-mediated mechanosensing would be a significant factor in ensuring successful cytokinesis. We found that dividing cells are exquisitely sensitive to mechanical stress inputs, relocating myosin II to sites of the externally imposed stress. This system has the hallmark of a soft mechanical checkpoint, slowing cytokinesis until the deformation is corrected. The myosin II-based mechanosensing is performed by a three-part sensor, including force amplification through the myosin II lever arm, myosin bipolar thick filament (BTF) assembly, and actin filament anchoring by cortexillin I. Multi-scale modeling demonstrates how myosin II force-sensing and cooperative actin-binding couples to BTF assembly and quantitatively accounts for the amounts and kinetics of myosin mechanosensitive accumulation. Furthermore, forces are shared between myosin and different actin crosslinkers with myosin having potentiating or inhibitory effects on certain crosslinkers. Additionally, different types of cell deformations elicit distinct responses: myosin and α-actinin respond to dilation while filamin mainly reacts to shear. This myosin II-based mechanosensory system is part of a larger control system that tunes myosin accumulation at the cleavage furrow under diverse mechanical constraints. In this context, cortexillin I not only anchors the actin filaments, but also links to signal transduction proteins. These signaling proteins, including IQGAPs and the chromosomal passenger complex proteins, reinforce 'normal' signals that emanate from the mitotic spindle to direct myosin II accumulation. Overall, this control system demonstrates how mechanical inputs can be converted to signaling outputs in a manner analogous to chemical signal transduction.

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Vimentin Affects Actin Network Percolation and Mechanics
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The mechanics of the cytoskeleton are determined largely by actin, microtubules, and intermediate filaments. In vitro, composite actin/microtubule networks and actin/myosin networks have revealed unexpected emergent features, suggesting that cytoskeletal mechanical behavior is greater than the sum of its parts.
Here, we construct in vitro composite networks of actin and the intermediate filament vimentin, and study the composite network mechanics using bulk rheology. When using biotin-neutravidin as an actin crosslinker, we find that